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Editorial

Short review of randomized controlled trials (RCTs) for Surgical Neurology International: Two important RCT articles for 2018 – Part I

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Two methodologically sound randomized controlled trials (RCTS) were published in the first quarter of 2018 dealing with thrombotic stroke and intracranial aneurysms. Both RCTs offer significant scientific findings which may be of interest to the readers of Surgical Neurology International who may wish to incorporate the articles' recommendations into their practices.

(1) Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, *et al.* Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018;378:708-18.

The DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) trial is a 38 center, open-label trial utilizing blinded outcome assessment. This RCT compared thrombectomy versus medical therapy in the management of 182 patients – 92 endovascular and 90 medical therapy. Patients included in the study had either internal carotid artery or middle cerebral artery (M1) thrombotic occlusions, with ictal onset between 6 and 16 hours prior to presentation. All patients had to exhibit radiologically defined salvageable ischemic brain tissue that had not yet infarcted, with infarcted volumes less than 70 mL, and ratio of volume of ischemic to infarct volume had to be greater than 1.8. Comparing the two groups, the DEFUSE 3 trial found significantly higher rates of survival post thrombectomy (77 out of 90 patients) versus 67 out of 90 patients receiving medical therapy alone. Furthermore, those undergoing thrombectomy exhibited significantly greater likelihoods of 90-day functional independence (41 out of 90 post thrombectomy) versus just 15 out of 90 treated with medical therapy alone.

Several statistically valid key points were emphasized by this methodologically strong RCT:

(1) more wake up strokes (with potentially unclear exact time of stroke onset) were included in the thrombectomy group (n = 49) versus medical therapy group (n = 42),
(2) thirteen heterogeneous patients (that is, small numbers per center) with internal carotid artery artherosclerotic plaques additionally received cervical angioplasty and stent placements,
(3) thirty-four thrombectomy patients versus 28 in the medical therapy group had atrial fibrillation. They, therefore, had potentially different underlying clot textures than those with atherosclerotic artery-to-artery thrombi,

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(4) up to 10–15% of patients after thrombectomy experienced symptomatic reperfusion hemorrhages (6 out of 90 patients), with an additional 8 patients who experienced parenchymal hemorrhages occupying more than 30% of the stroke volume, and
(5) technically, there were inter-center differences in the calculations of ischemic and infarct volumes based on each center's CT and MR perfusion protocols, and stroke patients' cardiac outputs.

Conclusion

This multicenter RCT compared patients undergoing thrombectomy versus standard medical therapy alone for strokes including those with wake-up strokes, attributed to embolic M1 and ICA occlusions. They significantly demonstrated that thrombectomy was safe for up to the 6–16-hour window. Furthermore, they demonstrated potentially higher rates of survival and functional independence for those with radiologically defined salvageable ischemic brain tissue (not yet infarcted). Similar findings were noted in a recent Bayesian adaptive multicenter trial (DAWN trial, Nogueira *et al*.) for patients who underwent stent-assisted clot retrieval within the same time frame, also resulting in a comparable number of post-thrombectomy symptomatic reperfusion hemorrhages.[1] On the basis of these RCTs, the indication for mechanical thrombectomy has been expanded in the 2018 AHA/ASA guidelines.[2] For selected patients with acute ischemic stroke within 6 to 16 hours of the last known normal clinical state who have large vessel occlusion in the anterior circulation and who meet other DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended as Grade I evidence. Further studies are required to examine the incidences of post-thrombectomy-related reperfusion complications and its safety and efficacy, as the thrombectomy time window extends up to and beyond 16–24 hours.

1. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018;378:11-21.
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al*. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American heart association/American stroke association. Stroke 2018;49:e46-e110.

(2) Gathier CS, van den Bergh WM, van der Jagt M, Verweij BH, Dankbaar JW, Müller MC, *et al*. Induced hypertension for delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: A randomized clinical trial. Stroke 2018;49:76-83.

This study by Gathier *et al*. was a four-center, single-blind, RCT from Netherlands. The authors reported that induced hypertension for aneurysmal subarachnoid hemorrhage patients in those showing delayed cerebral ischemia did not improve cerebral perfusion, and may additionally be associated with increased side effects. From 2009 to 2015, a 20-patient cohort with delayed cerebral ischemic (1-point decrease on Glasgow Coma Score, with new neurological deficits for more than 1 hour) was randomized to receive induced hypertension therapy with fluids and norepinephrine. They were compared with 20 patients in the control group not receiving induced hypertension. The former patients' "endpoints of symptomatic improvement" utilizing maximal mean arterial pressures of 130 mmHg were assessed. Norepinephrine infusions were continued for 48 hours prior to tapering; doses were adjusted during the tapering period if new symptoms appeared. For the 20 patients with induced hypertension versus 20 control patients, poor functional outcomes (modified Rankin score > 3) were noted in 12 patients versus 8, with 6 versus 4 deaths, respectively. Alternatively, 12 patients in the induced hypertension versus 6 control patients experienced clinical improvement. Notably, for those receiving inotropic blood pressure augmentation, 2 patients experienced myocardial infarction, 1 developed atrial fibrillation, and 2 cases had pneumothorax from central venous line insertion. The trial could not reach the target number of 120 patients per group due to slow recruitment, therefore, a longer term follow-up study is warranted.

Conclusion

This multicenter trial gives further insight into the results of utilizing induced hypertension to treat delayed vasospasm (that is, delayed clinical ischemic deficits) in patients with aneurysmal subarachnoid hemorrhage. Notably, it did not document the safety or efficacy of using norepinephrine and fluids to augment blood pressure in these patients. Other ongoing clinical trials are investigating whether administering other vasodilator agents utilizing different routes (for example, intravenous versus intrathecal milrinone) would safely alleviate vasospasm without incurring significant concomitant cardiac and/or other systemic morbidity.